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Association between renal function, rehabilitation outcome and survival in older patients discharged from inpatient rehabilitation

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Abstract

Background

Chronic kidney disease (CKD) is common in older people, but it is unclear if it affects survival and rehabilitation outcomes independent of comorbidity and physical function in this population.

Study Design

Cohort analysis of prospective, routinely-collected, linked clinical datasets.

Setting and participants

Patients discharged from a single inpatient geriatric rehabilitation centre over a 12 year period

Predictors

Admission CKD stage as a predictor of improvement in Barthel score during rehabilitation; discharge CKD stage and 20 point Barthel activities of daily living score as predictors of survival post-discharge.

Outcomes

Survival post-discharge was modelled using Cox regression analyses, unadjusted and adjusted for age, sex, morbidities (ischaemic heart disease, chronic obstructive pulmonary disease, stroke, diabetes and heart failure), Barthel score and CKD stage on discharge, serum calcium, haemoglobin and albumin levels. The effect of admission CKD stage on the change in Barthel score during admission was modelled using analysis of covariance, adjusted for admission CKD stage, Barthel score and comorbidities.

Results

3012 patients were included, mean age 84 years. 2394 patients died during mean follow-up of 8.3 years. Compared to patients with a glomerular filtration rate of 60-90ml/min/1.73m², adjusted hazard ratios for death were: CKD3a 1.26 (95%CI 1.13, 1.40), CKD3b 1.45 (95%CI 1.29, 1.63), CKD4/5 1.68 (95%CI 1.42, 1.99). The relationship between discharge Barthel score and survival was similar within each discharge CKD category (HR 0.95 per Barthel score point within eGFR>90ml/min/1.73m²; HR 0.93 in eGFR 60-90; HR 0.92 in 45-60; HR 0.95 in 30-45 and HR 0.90 in <30ml/min/1.73m²; p=0.19 for interaction). Similar improvements in Barthel score between admission and discharge were seen for each admission CKD category.

Limitations

Single centre study using routinely collected clinical data

Conclusion

CKD stage and Barthel score are independent risk markers for survival in older rehabilitation patients, but advanced CKD does not preclude successful rehabilitation.

Introduction

Chronic Kidney Disease (CKD) increases in prevalence with advancing age. Between 31 and 45% of people over the age of 70 have CKD of Kidney Disease Improving Global Outcomes (KDIGO) stage 3a or worse^{1,2}. This decreased renal function is associated with increased all cause and cardiovascular mortality even in people over 75 years of age³. Although impaired physical function appears to be a risk marker for mortality in younger CKD patients⁴, it is less clear in older patients whether decreased renal function and impaired physical function are independent risk markers for mortality, or whether low glomerular filtration rate merely reflects frailty or impaired physical function – themselves both powerful markers for mortality in older people⁵. Clarifying this issue is important, firstly in deciding whether labelling very old patients as having CKD serves a useful purpose, and secondly in considering whether intervening to ameliorate declines in renal function in the oldest old are likely to translate into clinically relevant benefits. This is of particular importance given that end-stage renal failure is a comparatively less common mode of death in older CKD patients³.

Poor physical function and decreased exercise capacity have been found to exist in patients with CKD, and recent studies suggest that patients with CKD are both more likely to be frail⁴ and to undergo more rapid decline in physical function⁶. This close relationship between CKD and physical function suggests that incorporating measures of physical function into analyses of outcome for older CKD patients is thus important. It also raise the question of how the presence of CKD impacts on the ability of older people to rehabilitate following illness.

We therefore undertook an analysis to examine the effect of CKD on mortality in very old patients, accounting for the effect of physical function. We also aimed to examine the effect of CKD stage on the ability of older people to successfully rehabilitate after illness.

Methods

Study population

The study cohort was derived from a group of older patients who underwent inpatient rehabilitation over a 12 year period (from January 1999 to December 2011) in the Dundee Medicine for the Elderly service; details of the service and of a subset of the cohort have been published previously⁷. Patients were transferred to the rehabilitation unit after recovery from acute illness including stroke, fractures, general medical or general surgical illness. Data on routinely collected rehabilitation outcomes for the cohort includes the 20 point Barthel score (a measure of activities of daily living)⁸ at admission and discharge. These data were linked to data held by the University of Dundee Health Informatics Centre (HIC) on a range of other routinely collected healthcare measures⁹. Information on biochemistry and haematology results, hospitalisation data and diagnoses (Scottish Morbidity Register 01) coded using ICD-10 codes were accessible in the linked dataset. Dates of death, derived from the Scottish Government Records Office, which records all deaths registered within Scotland, were also held by HIC in the linked dataset. For this analysis, data from the first admission to the rehabilitation service were used. Analyses of improvement in rehabilitation were confined to those who had an admission and discharge Barthel score recorded; survival analyses were confined to those alive at discharge from rehabilitation who had a discharge Barthel score recorded. A flowchart depicting the derivation of the analysis cohort is given in Figure 1. Data Protection Office (Caldicott Guardian) approval was obtained prior to data linkage and analysis, but institutional review board approval was waived in view of the routinely collected nature of the data.

Exposure and Outcome measures and covariates

Time to death was calculated as the time between the date of discharge from rehabilitation facility to the date of death as recorded in Scottish General Records Office death records. The 20 point Barthel score was recorded as part of routine care by the multidisciplinary rehabilitation team. The Barthel score is a measure of basic activities of daily living (ADL); it records what a person is capable of doing across ten activities: walking, transfers, feeding, bathing, grooming, dressing, bowel function, bladder function, toilet use and stair use⁸ (score ranges from 0-20 where 20 = highest level of independence) . It is widely used as a measure of basic ADL's in older people, and previous work in this cohort has shown that a 1 point difference between admission and discharge on the Barthel score relates to a 5-10% difference in mortality⁷.

All biochemical indices were taken from routinely collected clinical data, held by HIC. All analyses were performed in a single laboratory (Biochemical Medicine, NHS Tayside). The measurement taken closest to the date of admission to rehabilitation was used in analyses of the effect of CKD stage on change in Barthel score during rehabilitation. For post-discharge survival analyses, the measurement taken closest to the date of discharge from rehabilitation was used. Creatinine was measured using a compensated, rate-blanked method on a Roche multichannel analyser; the methodology was traceable to IDMS. In February 2007, a new algorithm for creatinine calculation was introduced locally to align results with UK NEQAS results. Results in our database prior to this point were corrected in our analyses using the equation: Creatinine = (old creatinine x 1.1358)-26. Estimated GFR was derived from creatinine measures using the CKD-EPI equation¹⁰. Renal function was then categorised on the basis of the KDIGO chronic kidney disease classification¹¹ (>90 ml/min; 60-89 ml/min; 45-59 ml/min; 30-44 ml/min; 15-29 ml/min and <15 ml/min). Data on proteinuria was not available and hence was not included in analyses; only a small proportion of patients had phosphate or bicarbonate measurements performed as these analytes were not part of standard biochemistry panels; these analytes are therefore not included in the analyses. Specific morbidities (ischaemic heart disease, stroke, heart failure or COPD) were coded from ICD-10 codes on the basis

of previous hospitalisations for myocardial infarction, stroke, and heart failure. Diabetes status (present or absent) was taken from linked data from the Scottish Care Information – Diabetes Collaboration (SCI-DC) database¹², also held by HIC. Cancer diagnosis in the five years prior to rehabilitation admission was taken from the Scottish Cancer Registry (SMR06) records, held by HIC.

Data analysis

Descriptive statistics were generated for each category of eGFR; values in each category were compared to the reference group (eGFR>90ml/min/1.73m²) using ANOVA for continuous variables and either Pearsons chi-square or Fishers exact tests for categorical variables. Two main analyses were undertaken. The first compared renal function category with the improvement in Barthel score from admission to discharge. The group with eGFR 60-90ml/min/1.73m² were used as reference, and each category of renal function was compared with the index group using ANOVA, both unadjusted and adjusted for a range of covariates

The second analysis used Cox regression analysis to compare the risk of death between different categories of renal function. Both unadjusted models and models adjusted for a range of covariates were developed; adjusted models all used forced entry of covariates, which were selected a priori on the basis of biological plausibility. Covariates used in the analysis were age, sex, previous hospital admission for myocardial infarction, stroke, heart failure, or COPD, presence of diabetes mellitus, admission Barthel score, previous cancer diagnosis, serum calcium, serum albumin and haemoglobin. Follow up was censored at 23rd July 2012. To formally test for interaction between estimated GFR and discharge Barthel score on survival, both terms were entered into the adjusted Cox regression model as continuous variables, along with an interaction term. All statistical methods were performed with SPSS version 22 (IBM, New York, USA). A two-sided p value of <0.05 was taken as significant for all analyses.

Results

The full cohort consisted of 4382 patients undergoing their first admission for inpatient rehabilitation. Of these, 373 died during their inpatient stay and were excluded from the analyses. No participants were of African or African-American ethnicity. Death rates during rehabilitation varied across eGFR category, being similar in groups with eGFR >90, 60-89, 45-59 and 30-44 ml/min/1.73m² (death rates 9.2%, 7.6%, 7.9% and 8.7% respectively) but higher for those groups with eGFR 15-29 and <15 ml/min/1.73m² (15.0% and 37.5% respectively). Given the small numbers of patients with eGFR<15, these patients were aggregated with those in the eGFR 15-29 category. 3012 patients were alive at discharge from rehabilitation and had data on all covariates, including discharge Barthel score; the mean follow up from date of discharge to the censor date for this group was 8.3 years (SD 3.4 years), with 2394 (79%) of patients dying during this follow-up period. Table 1 gives baseline data on this analysed study cohort. No patient in the study was undergoing renal replacement therapy during rehabilitation. During rehabilitation, CKD class did not change in 1966/3012 (65.3%), CKD class worsened in 406/3012 (13.5%) and improved in 640/3012 (21.2%)

Association of renal function with rehabilitation outcome

Table 2 gives the unadjusted and adjusted results of improvement in Barthel score during rehabilitation for each category of renal function, using the 2868 individuals with all covariates including admission and discharge Barthel scores. Patients with eGFR>90ml/min/1.73m² had slightly lower admission Barthel scores than the reference group, and improved slightly more during rehabilitation.

Association of renal function and functional status with survival

3012 individuals were included in this analysis; data on one or more covariates were missing for the excluded individuals. 2394 (79%) had died by the censor date of 23rd July 2012. Unadjusted and adjusted hazard ratios for survival, calculated using Cox regression analysis, are given in Table 3.

Worsening eGFR was associated with a greater risk of death as expected; within each eGFR category, higher discharge Barthel scores were associated with a lower risk of death. The relationship between discharge Barthel score and death was similar across all eGFR categories.

Interaction between Barthel score and eGFR on survival

Figure 2 shows the interaction between Barthel score and eGFR category, suggesting that Barthel score remained an independent predictor of outcome within each eGFR category. A formal test of interaction between eGFR and discharge Barthel score within the Cox regression analysis did not however reach significance ($p=0.19$)

Discussion

Our results show that in very old, functionally impaired people, both renal function and activities of daily living (an indirect measure of physical and psychosocial function) are independently associated with the risk of death, with a clear relationship between both severity of CKD and risk of death and ADL impairment and risk of death. This relationship is evident even with relatively mild impairment in renal function, and is still evident after adjusting for functional status as measured by the Barthel score; indeed the relationship between renal function and mortality is more pronounced in those with worse Barthel scores, suggesting that both factors contribute independently to the risk of mortality. We also found that in this group of older people, advanced CKD still derived benefit from rehabilitation, with similar improvements seen to those without advanced CKD. These findings support the current KDIGO guidance encouraging exercise for patients with CKD across all ages and severity categories¹³.

The relationship between CKD and mortality is well described, and this relationship extends to older patients^{14,15}. Debate continues as to whether CKD, especially less severe CKD (e.g. stage 3a) is a causal factor in older people or simply represents either normal ageing or a marker of disease burden, frailty and impaired homeostatic reserve^{16,17}. A weakness of previous studies is that few

have been able to adjust for measures of functional status in mortality analysis; the fact that CKD remained as a risk marker for mortality in our study even after adjustment for vascular disease and Barthel score suggests that CKD does not merely reflect functional impairment, but may lie on a causal pathway for functional impairment. Similar results were seen in a recent Korean study, which although only including small numbers of people with stage 3b, 4 or 5 CKD, suggested that the combination of low eGFR ($<60 \text{ ml/min/1.73m}^2$) and poor baseline ADL's was associated with significantly accelerated functional decline¹⁸.

The metabolic changes seen in advanced CKD have been linked to impaired physical function (e.g. reduced muscle function, grip strength and cognition). Previous work suggests that a worse degree of CKD is associated with a higher frequency of the frailty syndrome^{4,19} and a higher risk of functional decline over time^{20,21}. Systematically reviewed trial data confirms that exercise training can improve physical function in patients with CKD²², but few trials included very old participants, and it is not clear whether these benefits can be realised in inpatient rehabilitation services, especially given the higher risk of cognitive impairment, infection and vascular events, all of which can interfere with successful rehabilitation. Our results are therefore reassuring, suggesting that rehabilitation is likely to be effective for very old patients even with advanced CKD, and that CKD should not be used to limit access to rehabilitation. This is in accord with the current evidence that exercise and physical activity are beneficial for patients with CKD^{4,22}.

Disentangling causal relationships between CKD, functional impairment and mortality is difficult. CKD is strongly related to vascular disease, and vascular disease accounts for between one third and one half of the decline in physical function with age²³. Previous work has suggested common antecedents for both CKD and cognitive impairment in those aged 65 and over²⁴, and vascular disease is a prime candidate for such a common antecedent. Although vascular disease causes CKD, CKD in turn greatly accelerates the progression of vascular disease²⁵, due to a wide range of

pathophysiological processes including inflammation, oxidative stress, vascular calcification and the action of uraemic toxins. Other potential common antecedents include impaired vitamin D metabolism and the impact of oxidative stress on muscle, vascular and renal function.

Strengths and weaknesses

Our study has a number of strengths. The cohort were very old, with a high burden of comorbid disease, reflecting real-life practice. The use of routinely collected data also enhances the generalizability of the results as this population were not preselected for enrolment in a study. Use of a rehabilitation cohort allowed us to use a measure of functional status on a large number of patients; many previous studies have not been able to adjust for measures of physical function, which is critical in any analysis of outcomes in older people. The linked data available in the area of study allowed for inclusion of a range of biochemical and comorbidity variables.

A number of weaknesses also deserve comment. Routinely collected data are by their nature incomplete, and a number of variables of potential interest were either not collected (e.g. detailed measures of cognition, weight, blood pressure, walk tests and grip strength), or were collected on only a small, selected subgroup (e.g. bicarbonate and phosphate measures). We are unable therefore to derive a frailty score along the lines originally proposed by Fried et al²⁶. Similarly, low eGFR may reflect a higher burden of antecedent illness; the diagnostic coding that we used does not give information about illness severity, although we would expect this to be at least partly captured by the Barthel score. We used the CKD-EPI equation to estimate GFR; debate continues as to the relative merits of different methods of GFR estimation in very old people. The lack of weight data means that we are unable to adjust our estimates for very low muscle body mass; CKD-EPI is likely to overestimate eGFR in those with very low muscle mass. However, those with an eGFR of >90ml/min/1.73m² did not have a higher mortality rate than those with an eGFR of 60-90ml/min/1.73m², as would be expected if this was a major bias in our cohort. Cystatin C was not

measured as part of routine care in this cohort, hence we were constrained to using a creatinine-based measure. A recent large cohort study of patients aged 65 and over concluded that the CKD stage classification derived from CKD-EPI and MDRD4 was similar¹⁵. Some patients included in our study did not have stable kidney function, and hence the opportunity for misclassification arises. Our use of broad ranges of eGFR reduces the chance of misclassification based on changes between eGFR measurements however, and such changes after acute illness (both improvement and deterioration) reflect the complexity of managing older, frail patients with multimorbid disease, and hence reflect real-life clinical practice.

Another potential confounding factor in analysing renal function in older people is the loss of lean muscle mass (sarcopenia) with age. Although CKD-EPI partially adjusts for this loss by including age and sex in the equation, those with marked sarcopenia will have a disproportionately low muscle mass for their age and sex; these individuals will have been misclassified as having better renal function than they possess. Given that low muscle mass is a marker of increased mortality, the real relationship between impaired renal function and mortality may be even stronger than we observed, although our adjustment for Barthel score would be expected to at least partially reflect muscle mass. Whilst our results are applicable to those patients selected to undergo rehabilitation, they may not necessarily hold in fitter older people, or conversely in a general, older, frail population, not all of whom would be selected for rehabilitation after acute illness.

Our findings lend weight to the importance of CKD as an independent risk factor for mortality even in very old patients, confirm that even mild CKD (stage 3a) is a risk marker for mortality, and highlight that this relationship is most marked in the most functionally impaired patients. Observational studies cannot confirm causality however, and future work needs to focus on interventions to improve renal function or prevent decline in renal function, with a view to testing whether such interventions also improve functional status and reduce mortality in older people.

Additional studies examining the interplay between frailty, cognition and renal function in very old patients would usefully extend our current knowledge, as would examining markers of potential pathophysiological derangements (e.g. inflammation, oxidative stress and markers of vascular and metabolic health) that might cause both CKD and functional decline. Such studies need to focus on earlier stage CKD (stages 3a, 3b and 4) in older people, as these stages are both common in older people and hold out the best hope for preventative approaches before potentially permanent vascular, cognitive and functional harm has occurred.

Conclusion

Impaired kidney function is an independent contributor to increased mortality risk in the older population, however, it is not a barrier to successful rehabilitation even in the very old.

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of the study have been omitted, and that any discrepancies from the study as planned have been explained.

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Fig 1. Flowchart depicting selection of cohort for analysis

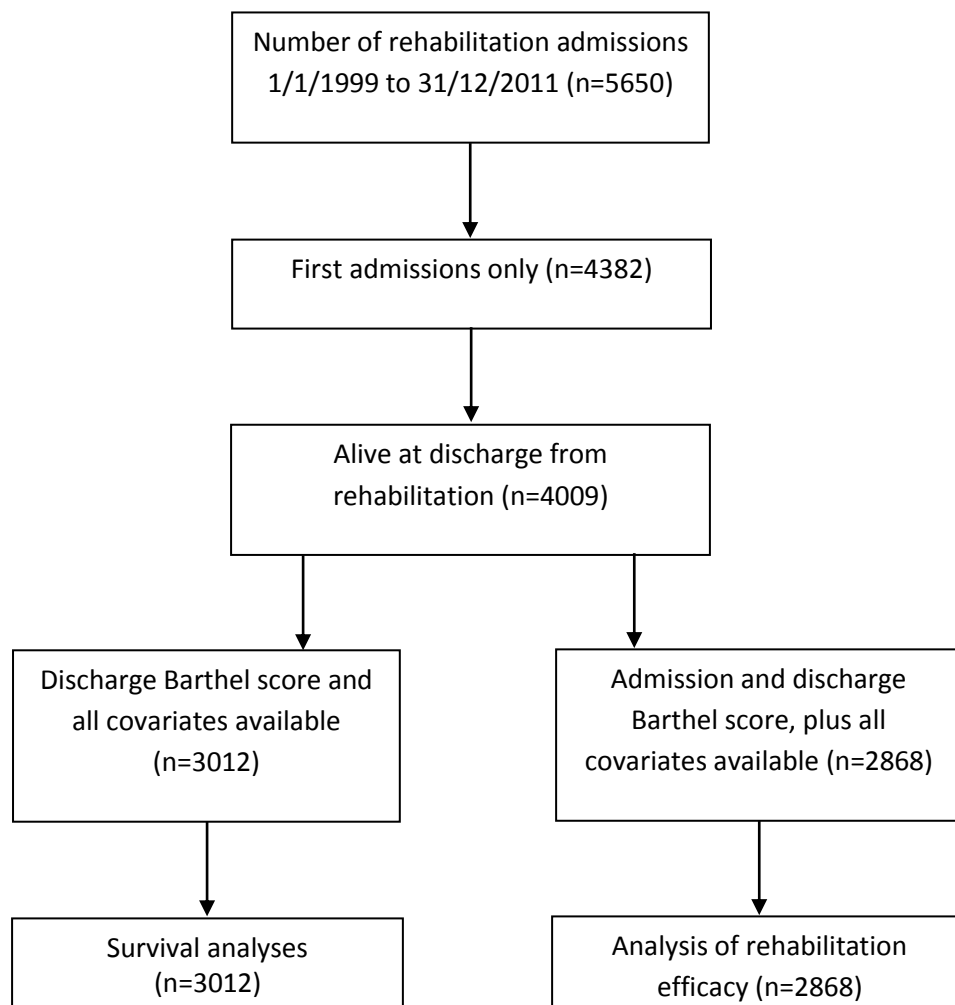


Table 1. Baseline details (n=3012) stratified by discharge eGFR category

| | Discharge eGFR category (ml/min/1.73m ²) | | | | |
|--|--|------------|--------------|--------------|--------------|
| | >90 | 60-90 | 45-59 | 30-44 | <30 |
| N (%) | 260 (9) | 1432 (48) | 652 (22) | 481 (16) | 187 (6) |
| Mean age (years) (SD) | 75.9 (6.5)** | 83.5 (7.0) | 85.6 (7.0)** | 87.1 (6.6)** | 86.7 (7.5)** |
| Male sex (%) | 164 (63)** | 622 (43) | 231 (35)** | 167 (35)** | 58 (31)** |
| Admission Barthel score*** (SD) | 9.4 (4.4)** | 10.3 (3.8) | 10.7 (3.7)* | 11.0 (3.6)** | 11.0 (3.5)* |
| Discharge Barthel score (SD) | 13.4 (6.0)** | 14.3 (4.7) | 14.6 (4.6) | 14.9 (4.0)* | 14.1 (4.7) |
| Previous admission for myocardial infarction (%) | 35 (13) | 180 (13) | 129 (20)** | 102 (21)** | 37 (20)** |
| Previous admission for stroke (%) | 21 (8) | 86 (6) | 51 (8) | 29 (6) | 14 (7) |
| Previous admission for CHF (%) | 8 (3) | 56 (4) | 77 (12)** | 71 (15)** | 36 (19)** |

| | | | | | |
|--------------------------------------|-------------|-------------|--------------|--------------|--------------|
| Previous admission for COPD (%) | 58 (22)** | 193 (13) | 94 (14) | 56 (12) | 14 (7)* |
| Diabetes mellitus (%) | 42 (16) | 231 (16) | 116 (18) | 87 (18) | 46 (25)** |
| Serum albumin (g/L) (SD) | 35 (6)** | 37 (5) | 37 (4) | 37 (5) | 36 (5)* |
| Adjusted serum calcium (mmol/L) (SD) | 2.40 (0.12) | 2.40 (0.11) | 2.41 (0.14) | 2.40 (0.12) | 2.41 (0.13) |
| Haemoglobin (g/dL) (SD) | 12.3 (2.1) | 12.3 (1.9) | 11.9 (1.8)** | 11.6 (1.7)** | 11.2 (1.8)** |

*p<0.05 compared to eGFR 60-90ml/min/1.73m² category

**p<0.01 compared to eGFR 60-90ml/min/1.73m² category

***n=2868

COPD: chronic obstructive pulmonary disease. CHF: chronic heart failure. GFR: estimated Glomerular filtration rate

Percentages for total numbers do not add to 100% due to rounding

Table 2. Association between renal function and rehabilitation outcomes as measured using the Barthel score for activities of daily living (n=2868)

| Estimated GFR at admission (ml/min/1.73m ²) | N | Admission Barthel score (SD) | Unadjusted difference in Barthel score (95% CI) | Adjusted difference in Barthel score** (95% CI) | Median length of stay (days) (IQR) |
|--|------|---------------------------------|--|--|---------------------------------------|
| >90 | 256 | 9.5 (4.4)* | 4.6 (4.2, 5.1)* | 4.3 (3.8, 4.8)* | 42 (55) |
| 60-90 | 1272 | 10.3 (3.8) | 3.7 (3.5, 3.9) | 3.7 (3.5, 3.9) | 38 (47) |
| 45-59 | 583 | 10.9 (3.7)* | 4.0 (3.7, 4.2) | 4.0 (3.8, 4.3) | 32 (42)* |
| 30-44 | 512 | 10.8 (3.7) | 3.6 (3.3, 3.9) | 3.6 (3.3, 3.9) | 35 (42) |
| <30 | 245 | 10.7 (3.8) | 3.7 (3.3, 4.2) | 3.8 (3.4, 4.2) | 33 (41)* |

GFR: Glomerular filtration rate

*p<0.05 vs eGFR 60-90ml/min/1.73m² category

**adjusted for age, sex, myocardial infarction, stroke, heart failure, chronic obstructive pulmonary disease, diabetes, admission Barthel score, previous cancer diagnosis, serum calcium, serum albumin and haemoglobin

Table 3. Survival post-discharge by renal function category (n=3012)

| Estimated GFR on discharge (ml/min/1.73m ²) | N | Unadjusted hazard ratio (95% CI) | Adjusted hazard ratio * (95% CI) | Hazard ratio per unit of discharge Barthel score (95% CI)* |
|---|------|----------------------------------|----------------------------------|--|
| >90 | 260 | 1.14 (0.98, 1.33) | 0.86 (0.74, 1.01) | 0.95 (0.92, 0.97) |
| 60-90 | 1432 | 1 | 1 | 0.93 (0.92, 0.94) |
| 45-59 | 652 | 1.15 (1.04, 1.28) | 1.26 (1.13, 1.40) | 0.92 (0.90, 0.94) |
| 30-44 | 481 | 1.35 (1.21, 1.51) | 1.45 (1.29, 1.63) | 0.95 (0.93, 0.97) |
| <30 | 187 | 1.56 (1.33, 1.84) | 1.68 (1.42, 1.99) | 0.90 (0.86, 0.93) |

GFR: Glomerular filtration rate

*adjusted for age, sex, myocardial infarction, stroke, heart failure, chronic obstructive pulmonary disease, diabetes mellitus, previous cancer diagnosis, discharge

Barthel score, serum calcium, serum albumin and haemoglobin

Figure 2. Graph of hazard ratio for death by discharge Barthel score and renal function category

